Armed Forces College of Medicine

AFCM

:Prepared by

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Good Morning
Have a Nice Day

INTENDED LEARNING OBJECTIVES (ILOs)

By the end of this lecture the student will be ab

1. List the BG nuclei and the functionally associated centers.
2. Describe the role of the direct and indirect circuits in control of voluntary movement.
3. Illustrate the role of dopamine in both circuits.
4. Describe Parkinson's disease.
5. Explain the causes of rigidity and static tremors in Parkinsonian disease
6. Use Integrated basic knowledge of the basal ganglia in diagnostic reasoning of parkinsonism
7. Recognize neurodegenerative diseases.
8. Explain pathogenesis of Parkinson disease.

INTENDED LEARNING OBJECTIVES (ILOs)

By the end of this lecture the student will be to:

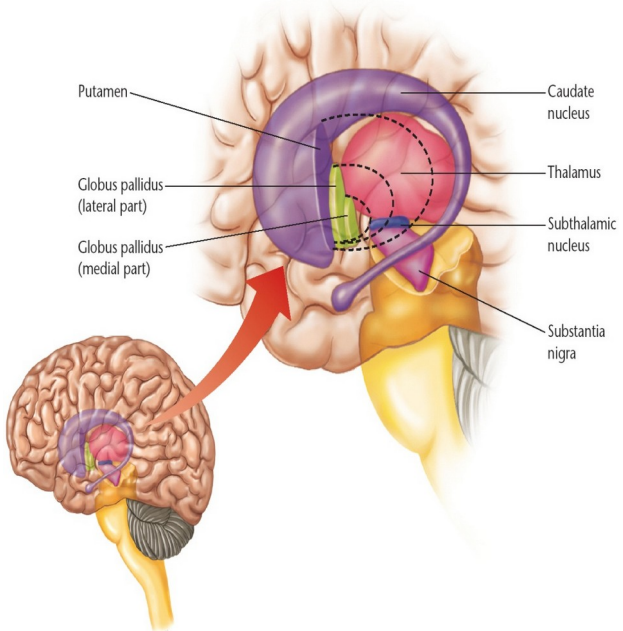
1. Analyse given data to diagnose pathological conditions of Neurodegenerative diseases of basal ganglia based on given clinical, radiologic data and/or laboratory findings
2. Recognize the antiparkinsonian therapy that aims to correct the dopamine/acetylcholine imbalance via the use of anticholinergic or dopaminergic drugs
3. Identify the mechanism of action of L-dop
4. Explain the important adverse effects of L-Dopa
5. Conclude the advantages of combination of L-Dopa with carbidopa

Lecture Plan

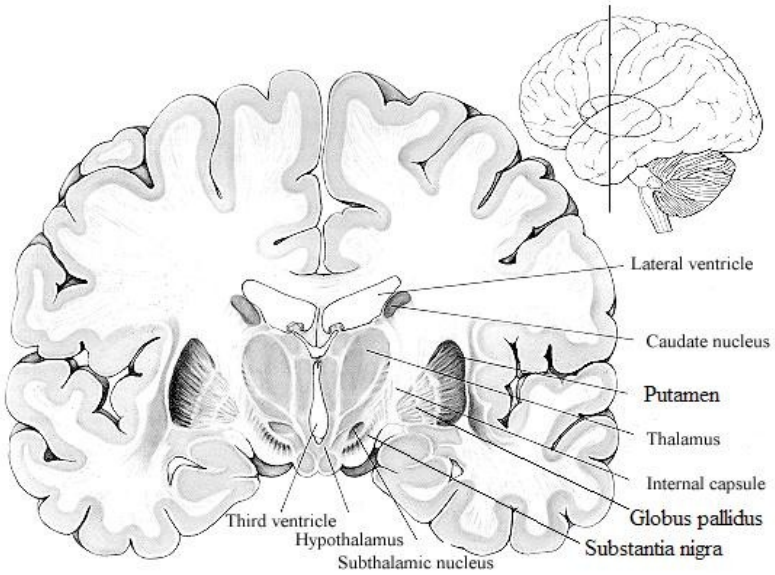
1. Functional anatomy and physiology of basal ganglia
2. Clinical manifestations
3. Mechanism of the disease
4. Pathology of the disease
5. Clinical scenarios
6. Management
7. Summary
8. Lecture Quiz

Physiology of the Basal ganglia

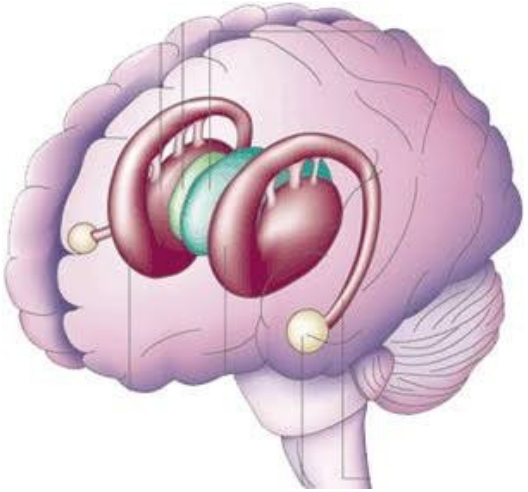
Anatomy of the Basal Ganglia



https://www.slideshare.net/drpsdeb/basal-ganglia-clinical-anatomy-physiology



https://scienceofparkinsons.com/2016/02/09/new-research-on-how-movement-is-controlled/



http://www.fmritools.com/kdb/grey-matter/basal-ganglia/index.html

Anatomy of the Basal Ganglia

•**Caudate nucleus.**

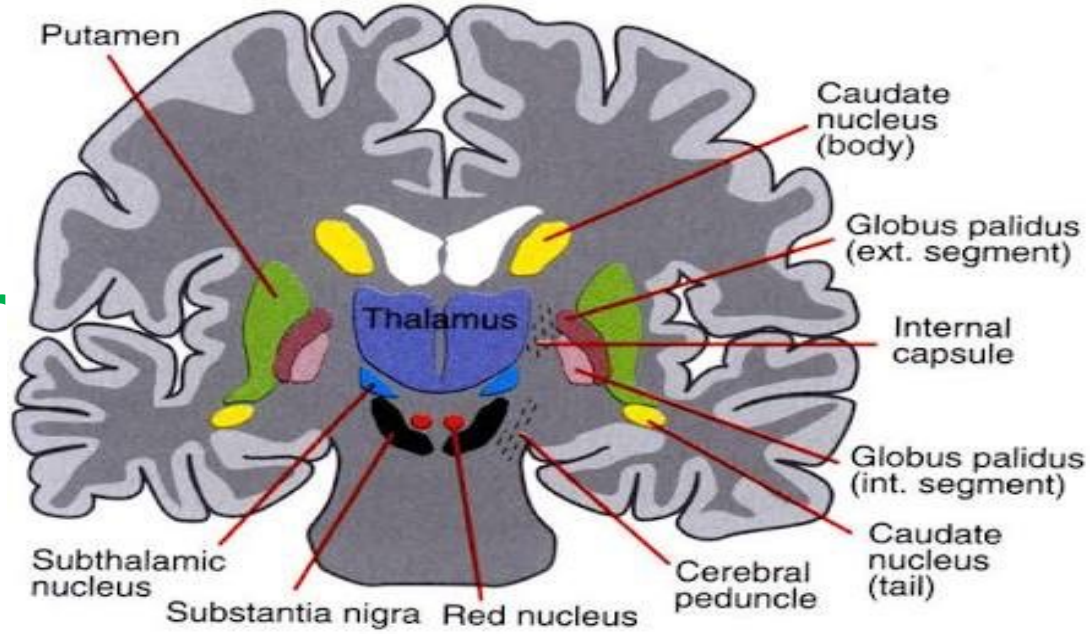
•**Putamen nucleus.**

Corpus Striatum

• **Globus pallidus:**

(internal and external parts)

Lenticular nucleus



https://www.intechopen.com/books/basal-ganglia-an-integrative-view/clinical-motor-and-cognitive-neurobehavioranships-in-the-basal-ganglia

•**Subthalamic nucleus.**

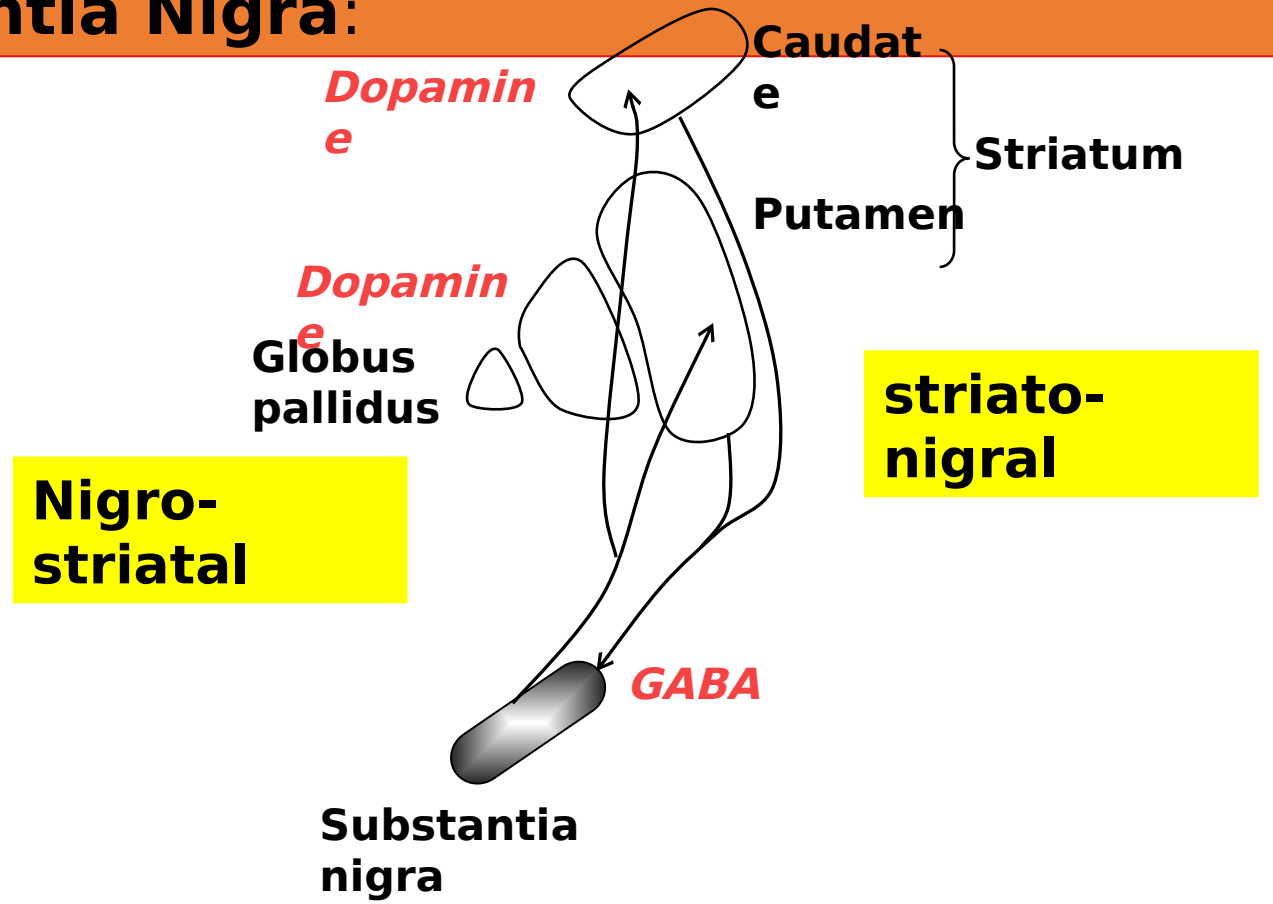
•**Substantia nigra.**

(pars compacta & pars

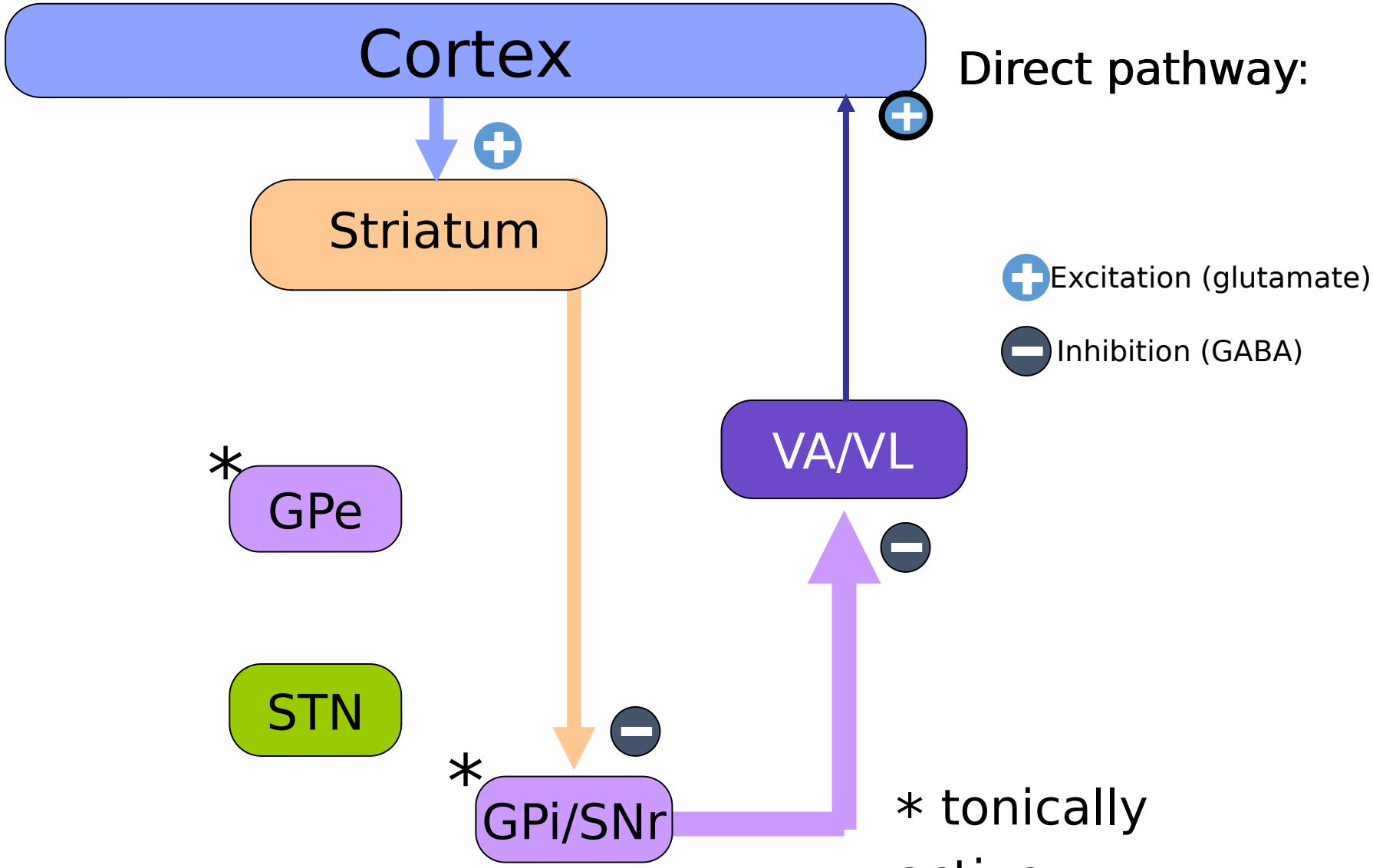
Neuronal Connections & neurotransmitters of the Basal Ganglia

(1) Internal connections

Connection between Striatum and Substantia Nigra:



Direct pathway



Direct pathway:

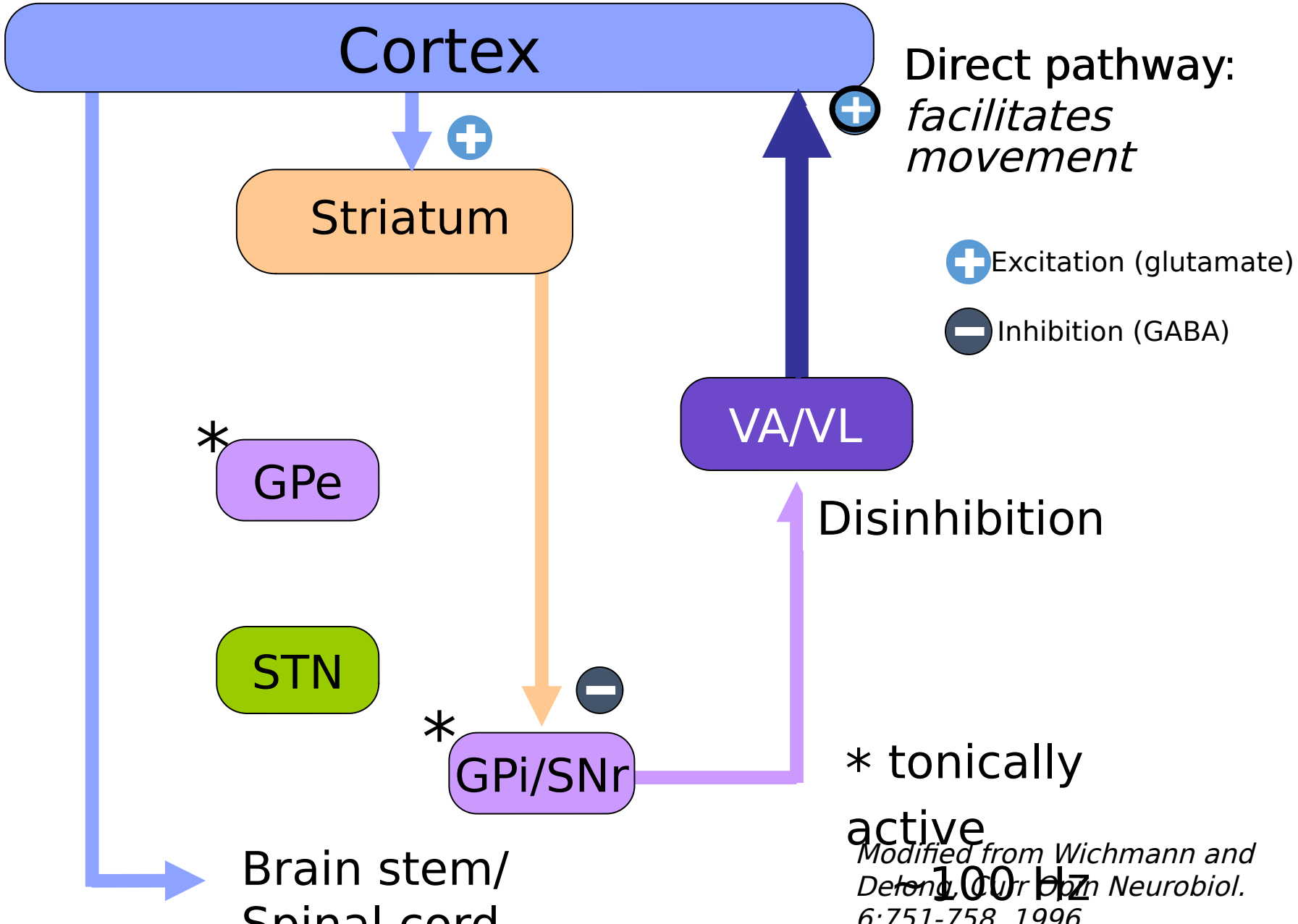
Excitation (glutamate)

Inhibition (GABA)

* tonically active ~100 Hz

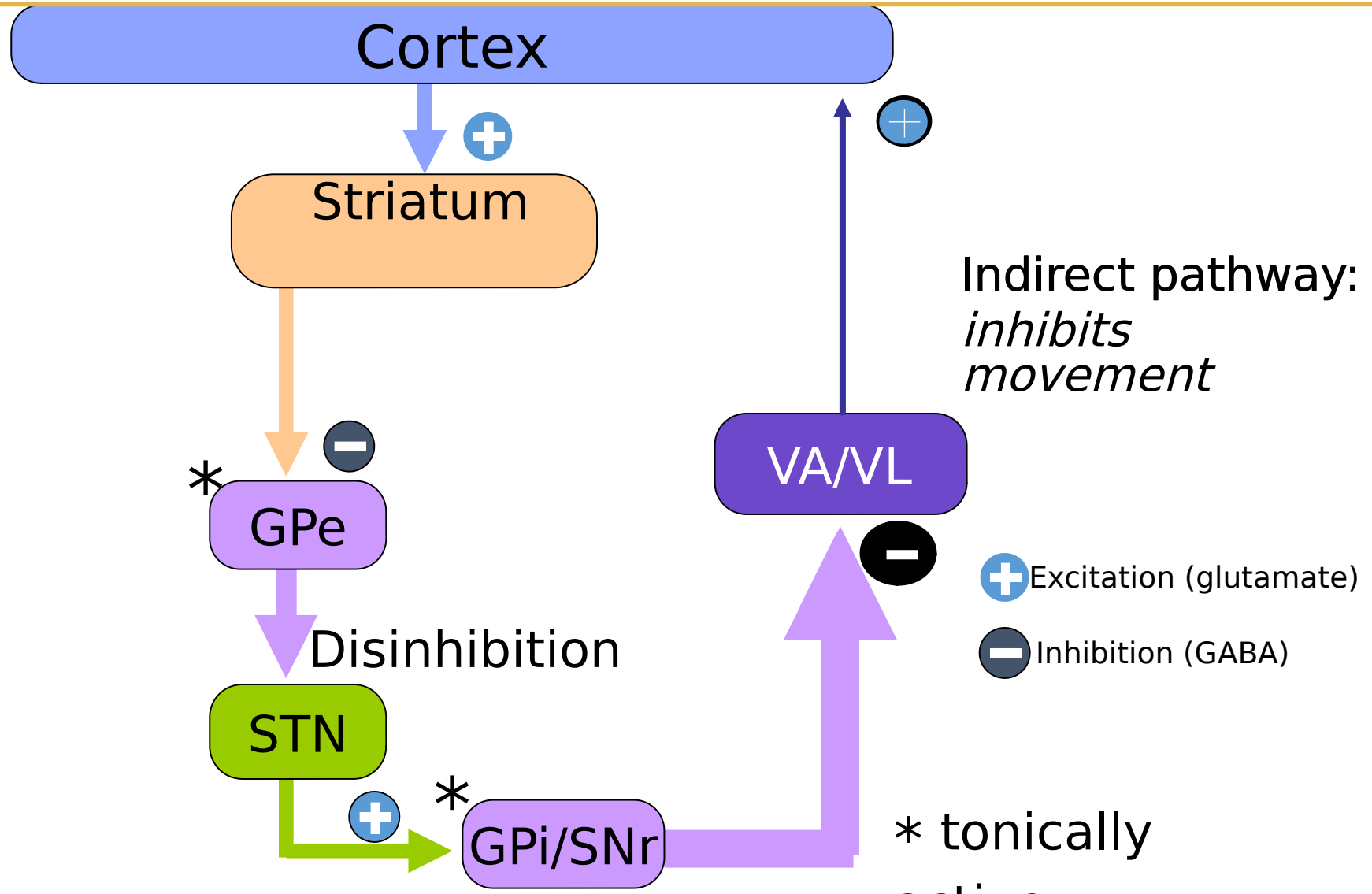
Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.

Direct pathway



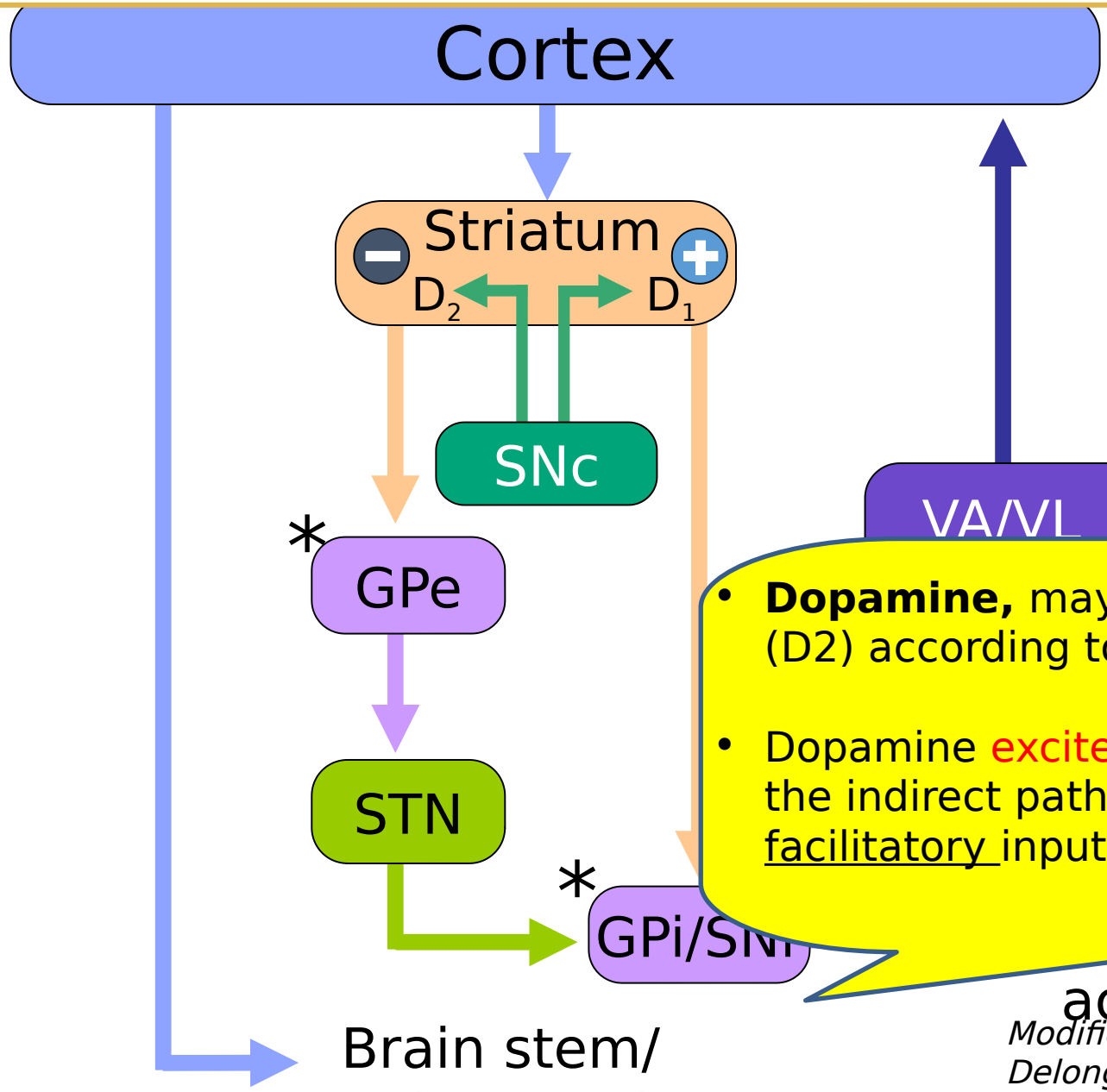
Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.

Indirect pathway



Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.

Role of dopamine in direct & indirect circuits



Direct pathway:
facilitates movement

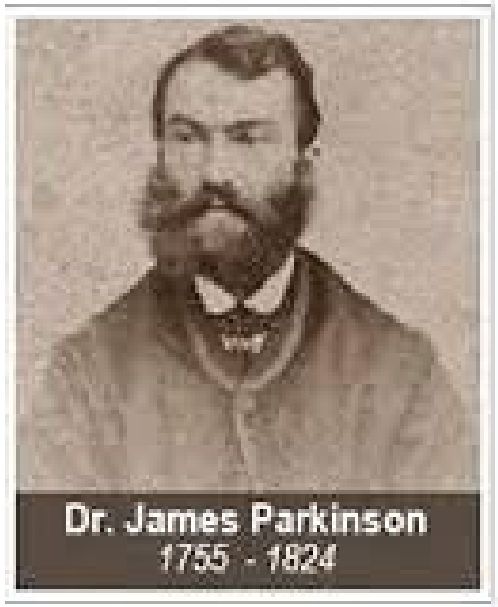
Indirect pathway:
inhibits movement

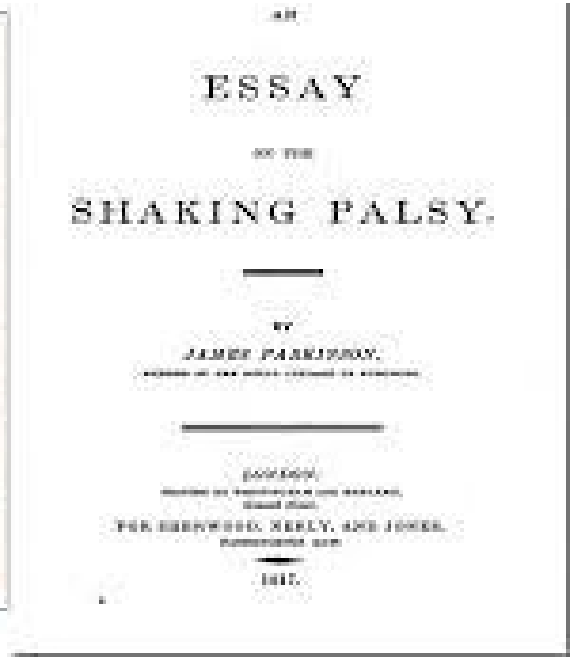
- **Dopamine,** may be **excitatory** (D1) or inhibitory (D2) according to the receptor.
- Dopamine excites the direct pathway and inhibits the indirect pathway, with a net effect to increase facilitatory inputs to the motor regions.

Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.

Bridging to clinical knowledge

Parkinson disease





AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

LONDON:

PRINTED BY SHERWOOD, NEELY, AND JONES,

1817.

- Parkinson’s disease (PD) is the second commonest neurodegenerative disease, exceeded only by Alzheimer’s disease (AD).
- Its cardinal clinical features were first described by the English physician James Parkinson in 1817.

Parkinsonism

- Parkinsonism is the most common of the extrapyramidal disorders and is characterized by **akinesia, rigidity**, **tremor**, and **postural instability.**
- Parkinsonism may be due to :

☑ Idiopathic PD

☑ Atypical parkinsonism

☑ Secondary parkinsonism

DD of Parkinsonism

Primary

Degenerative/inherited causes

- Idiopathic Parkinson’s disease
- Multiple system atrophy (MSA)
- Progressive supranuclear palsy (PSP)
- Dementia with Lewy body (DLB)
- Corticobasal degeneration (CBD)

Parkinson plus syndromes

DD of Parkinsonism

Secondary

- Repeated head trauma
- Infectious diseases: Postencephalitic PD and Neurosyphillis
- Drugs: typical antipsychotics Selected atypical, Antiemetics and Dopamine-depleting agents (reserpine, tetrabenazine)
- Toxins: Manganese, Cyanide, Methanol, Carbon monoxide
- Vascular: atherosclerotic disease

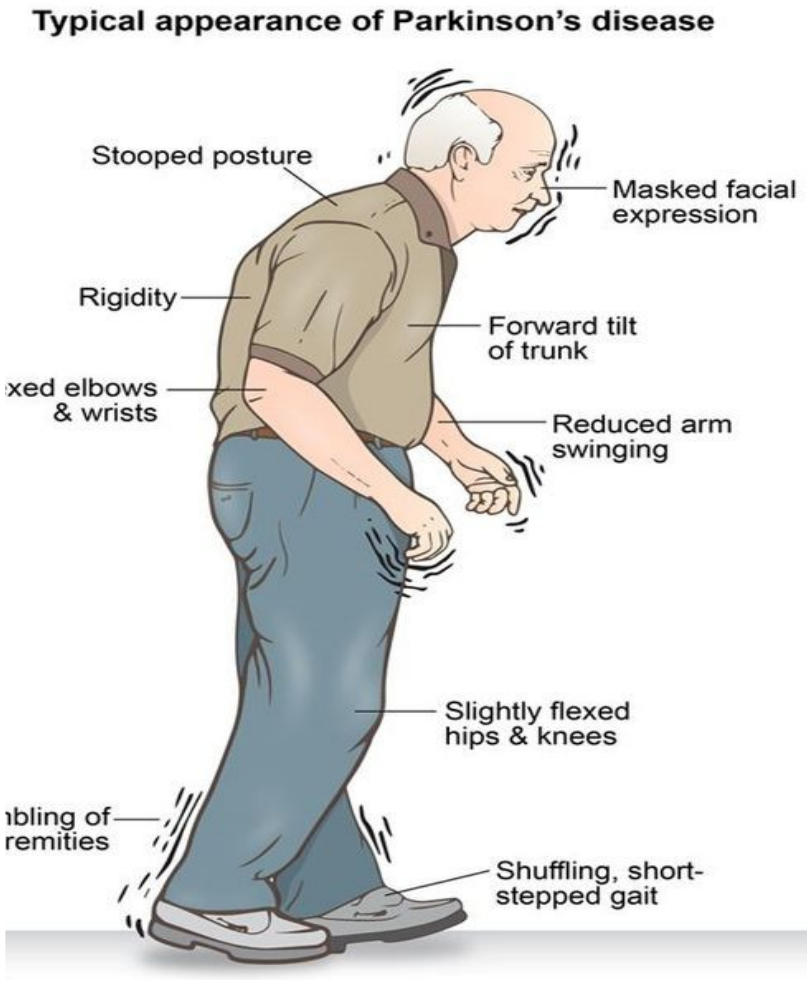
Parkinson disease

T

R

A

P



Atypical or Parkinson plus

Secondary parkinsonism

+

+

Other prominent feature

Underlying aetiology

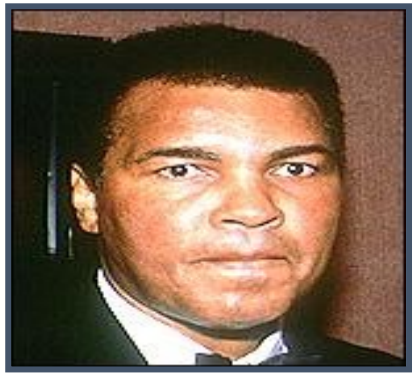
Mechanism of the disease

Parkinson’s disease = paralysis agitans

Cause

Loss of dopaminergic influence

Michael J. Fox



Muhammad Ali

Pope John Paul II

https://proteopedia.org/wiki/index.php/DOPA_decarboxylase

https://www.slideshare.net/CsillaEgri/cerebellum-and-basal-ganglia

Parkinson's disease = paralysis agitans

Characteristics

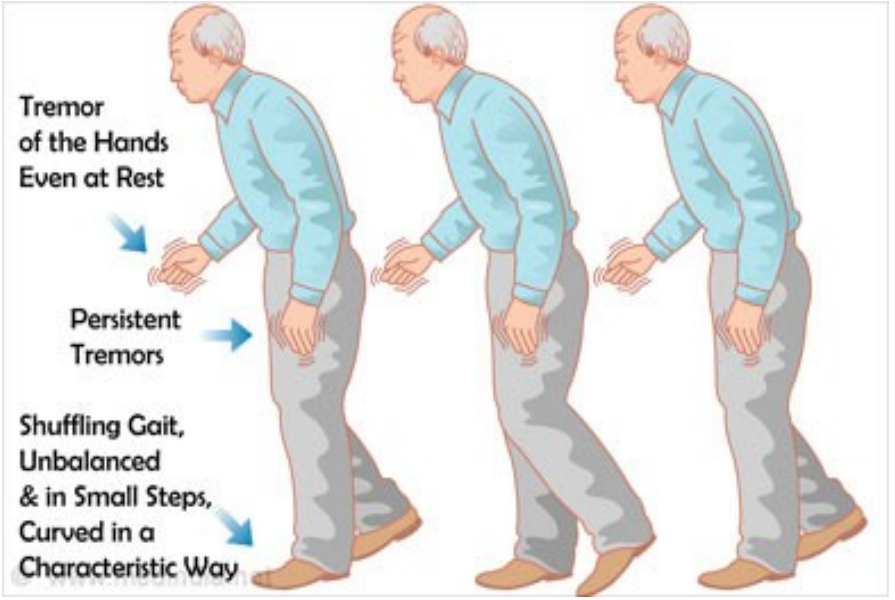
1- *Bradykinsesia / Akinesia*:

Bradykinesia: movements take longer time.

Akinesia: difficulty in initiating movement.

- ❑ **Monotonous speech**
- ❑ **Mask face**
- ❑ **Gait: short steps + shuffling**

loss of swinging arm movements

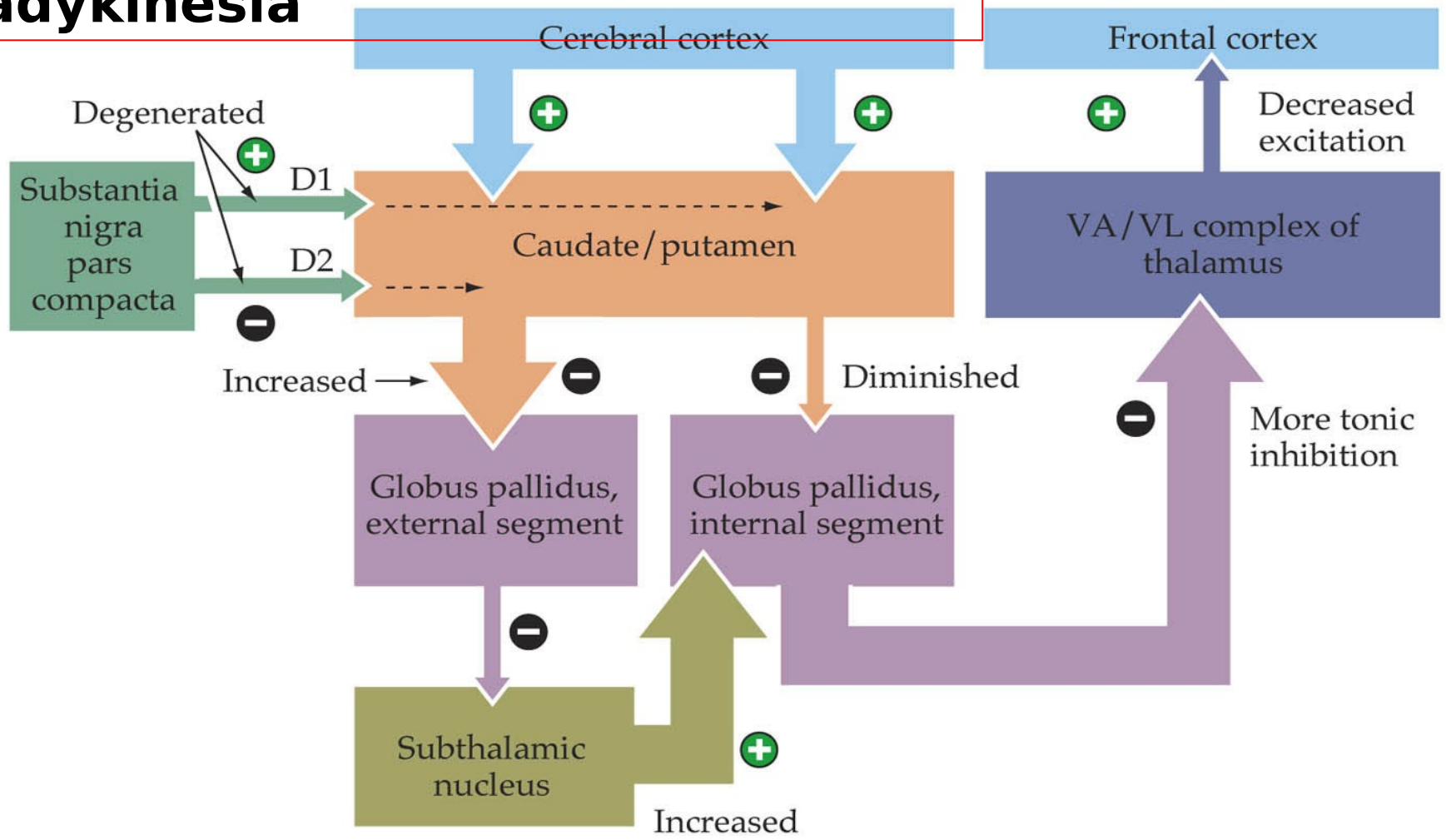


https://www.progressivecare.in/parkinsons-disease/

https://www.youtube.com/watch?v=j86omOwx0Hk

Parkinson's disease = paralysis agitans

Mechanism of Akinesia / bradykinesia



Mechanism of Akinesia / bradykinesia

- Difficult initiation of movement due to loss of facilitatory action of basal ganglia on the direct circuit of the muscles intended to move (action of dopamine on D1 receptors).

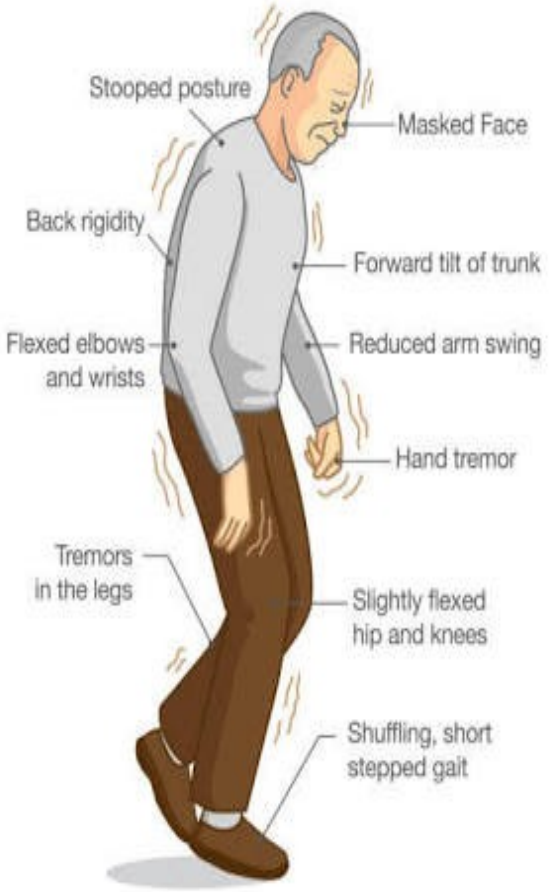
- The generalized rigidity of both agonist and antagonists.

- Associated loss of dopamine in the nucleus accumbens of the limbic system, which is supposed to have a role in motivation for motor activity

Characteristics

2- Rigidity:

- Increased impulses transmitted along the corticospinal tract to <u>both</u> α- and γ- motor neurons
- <u>lead pipe</u> rigidity or <u>Cogwheel</u> rigidity
- Flexors > extensors



https://practicalneurology.com/patients-caregivers/movement-disorders

2- Rigidity:

Rigidity versus spasticity

	Rigidity	Spasticity
1-Cause:	Facilitation of both types of the AHCs; the alpha(α) and gamma(γ)	**Facilitation of the gamma (γ) type only.**
2-Site:	Flexors mainly	**Antigravity muscles (upper limb flexors and lower limb extensors**
3-Attitude:	Generalized flexion	**Extended LL and flexed UL**
4-Reflexes:	Normal	**Exaggerated.**
5-Clonus:	Absent	**Present**
6-Lenghtening reaction:	Absent	**Present**
7-Management:	**Curable**	**Non curable.**

Characteristics

3- Tremors:

- involuntary rhythmic alternating contractions of antagonistic muscles
- Pill rolling at the hand or up & down movement of the mandible.
- frequency of 4-6/sec.
- Present at rest - disappear during voluntary movements

Parkinson's disease = paralysis agitans

Mechanism of hyperkinesia

- Basal ganglia has a normal net inhibitory effect on the motor cortex at rest (in between movements), yet, the exact mechanism is unknown.
- It is also one of the supraspinal inhibitory centers for muscle tone.
- Loss of the this inhibitory effect (imbalance between inhibitory dopamine and stimulatory acetyl-choline) leads to tremors.
- Decreased inhibitory effect on the muscle tone leads to

Pathology of the disease

Neurodegenerative Disease

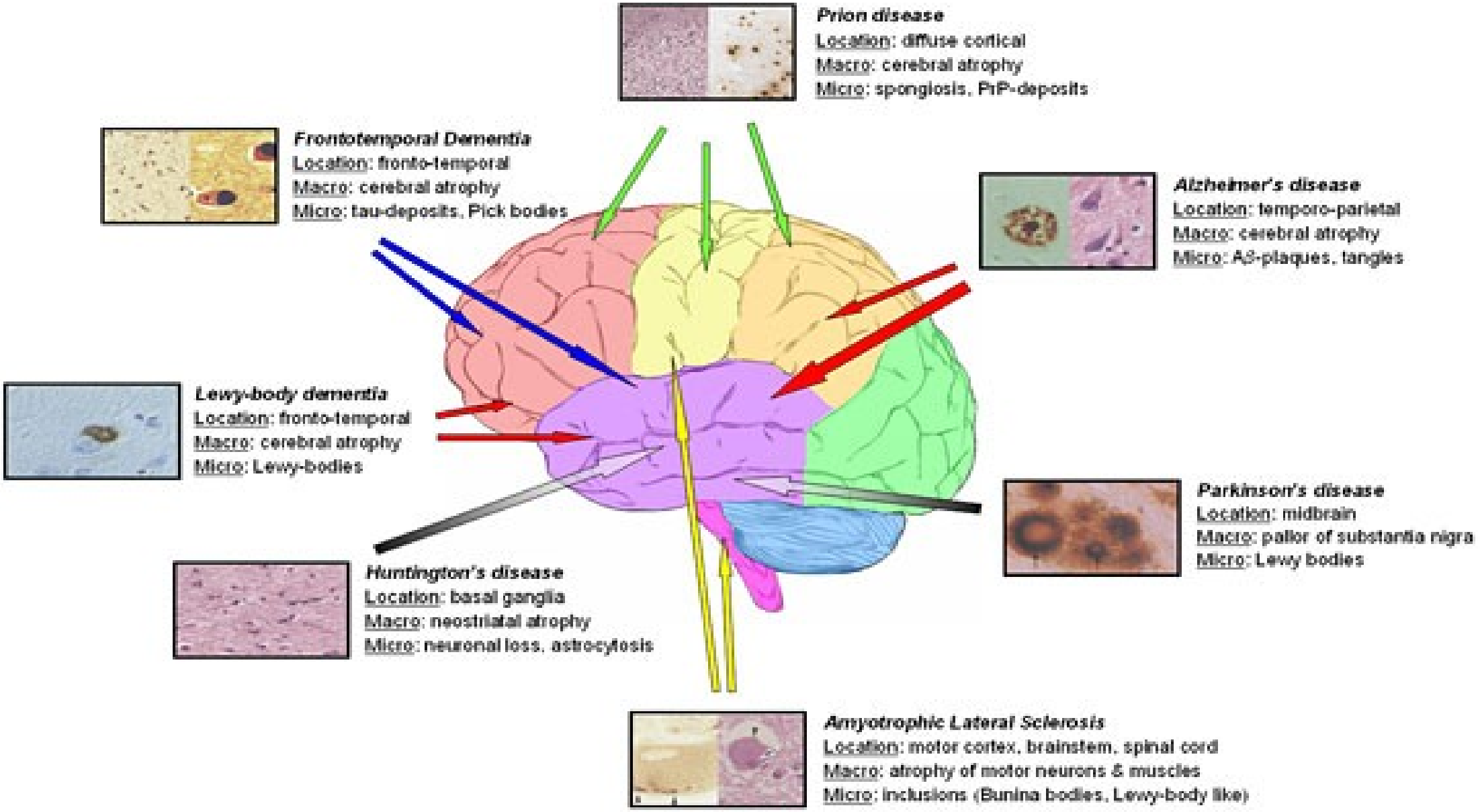
- **Most neurodegenerative diseases** shared the pathologic process of accumulation of **protein aggregates**, which serve as histologic hallmarks of specific disorders
- **Aggregates** may arise because of mutations that alter the **protein's synthesis or that disrupt pathways involved in processing or clearance** of the proteins.
- There may be **imbalance** between protein synthesis and clearance **(due to genetic or environmental factors)** that allows gradual accumulation of proteins.

Neurodegenerative Disease

Neurodegenerative diseases are characterized by the progressive loss of neurons.

- Different diseases tend to **involve particular neural systems** and therefore have relatively stereotypic presenting signs and symptoms:

- **Diseases that affect the basal ganglia** manifest as movement disorders; these may be **hypokinetic** as with **Parkinson disease** or **hyperkinetic** as with **Huntington disease**.



Bertram and Tanzi, *JCI*, 2005

https://www.nyas.org/media/3808/9c42c767-8619-46b1-b665-bd0e698879c3.jpg

Parkinson Disease

Parkinson disease (PD) is a neurodegenerative disease, associated with characteristic **neuronal inclusions containing α-synuclein protein** .

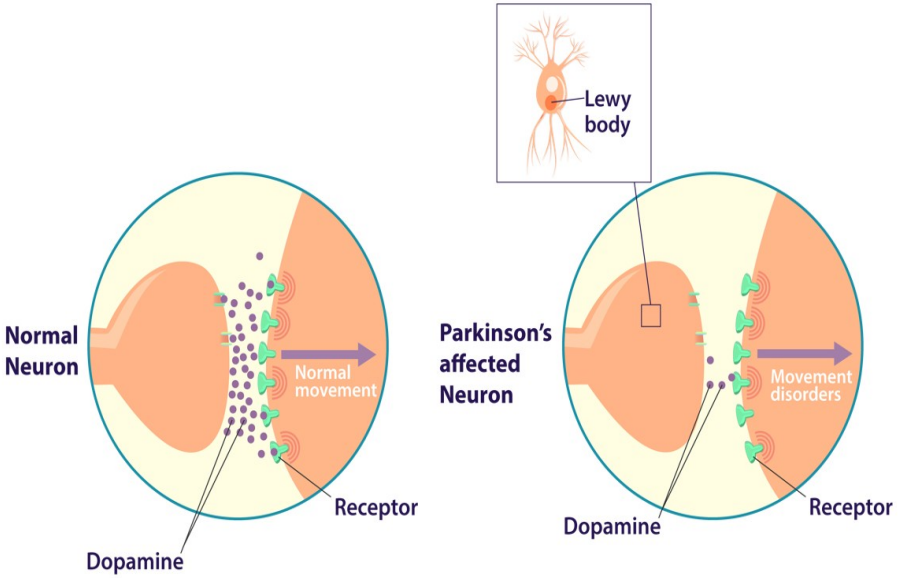
Parkinson Disease

Pathogenesis of Parkinson's Disease

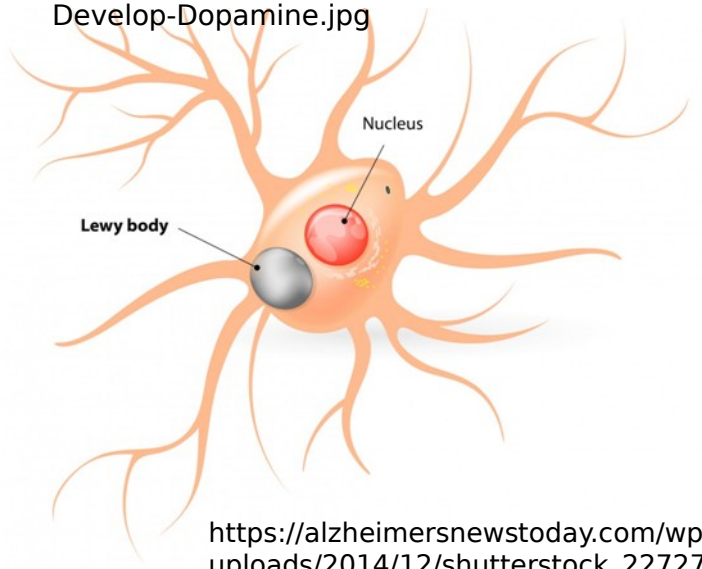
- **The *SNCA* gene (alpha-synuclein)** has been identified as a risk factor whi is involved in synaptic transmission.

- ***SNCA gene*** mutations and multiplications are associated with **familial PD**, but the **majority** of cases are **sporadic**.

- Even in sporadic PD, the diagnostic feature of the disease is the **Lewy body** which is an inclusion containing **α-**



https://parkinsonsdisease.net/wp-content/uploads/2017/04/How-Does-Parkinson%E2%80%99s-Disease-Develop-Dopamine.jpg



https://alzheimersnewstoday.com/wp-content/uploads/2014/12/shutterstock_227273575.jpg

Parkinson Disease

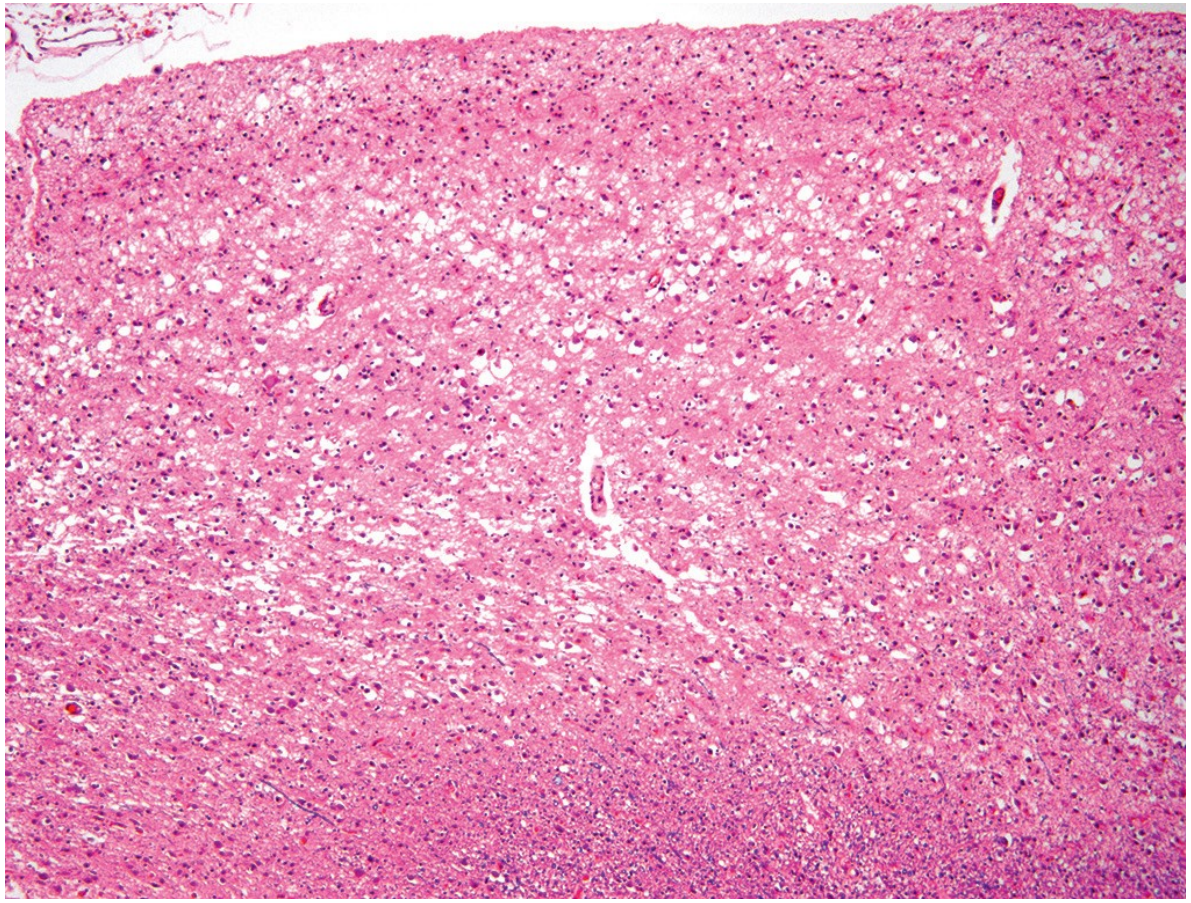
Gross examination:

There is **pallor** of the **substantia nigra**.

Microscopic examination:

1- **Loss** of pigmented **(dopaminergic) neurons** in the substantia nigra associated with gliosis.

2- Residual neurons show : **Lewy bodies**, which are intracytoplasmic round eosinophilic inclusions that

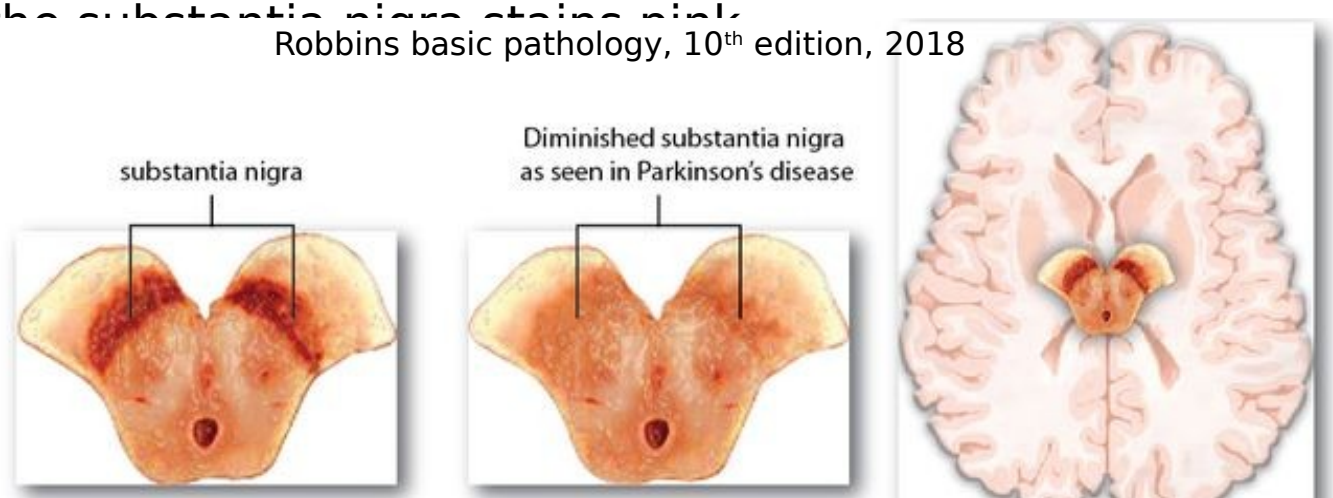


Severe neuronal loss and gliosis in the region of

Robbins basic pathology, 10th edition, 2018

(A) Normal substantia nigra. (B) Depigmented substantia nigra in idiopathic Parkinson disease. (C) Lewy body in a neuron from the substantia nigra stains pink

Robbins basic pathology, 10th edition, 2018



Clinical scenarios

Clinical vignette

- A 70-year-old male farmer was referred to a movement disorders outpatient clinic due to a 1-year non-disabling intermittent resting tremor of the left hand, that later progressed to the contralateral hand, he also noticed stiffness in the left arm.
- The patient’s face was expressionless (mask-like) and his movements were slow.
- On neurological examination the patient had normal cognition, cranial nerve and sensory examination.
- Motor examination revealed an intermittent mild resting tremor more on left side that resolves with active movement of the hand as well as mild slowing of fine rapid movement and signs of asymmetrical cogwheel rigidity

Clinical reasoning

A 70-year-old male patient presents with:

- ✓ Resting tremor with unilateral onset.
- ✓ Rigidity

→ **Unilateral Cog wheel rigidity**

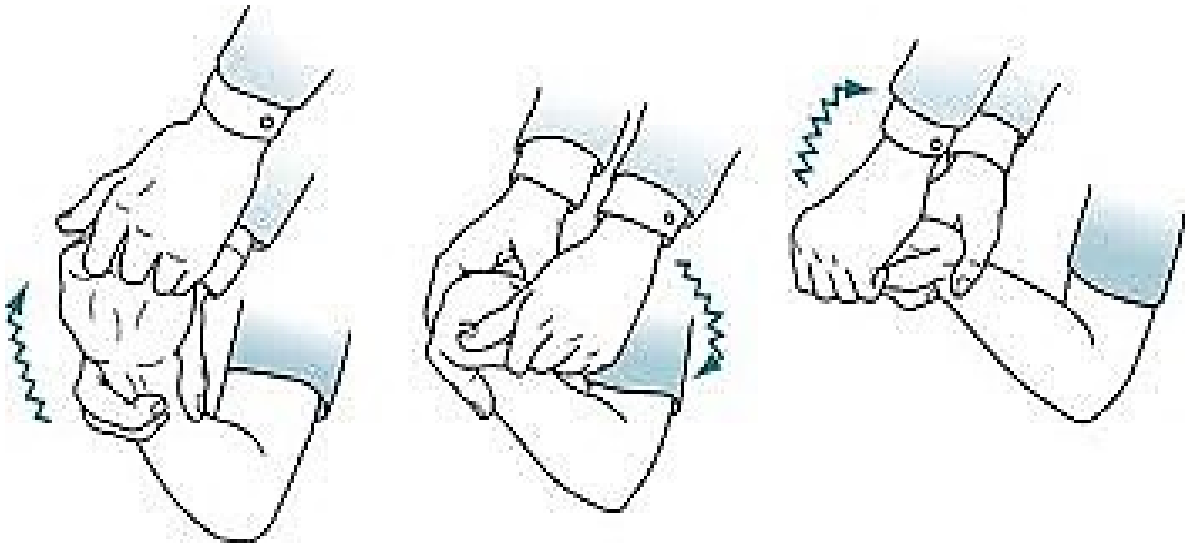
- ✓ Bradykinesia.
- ✓ Expressionless face (mask like)

These features are consistent with Parkinson’s disease

Clinical Picture

Positive motor

- Resting tremor: asymmetric 4-5 hz “pill-rolling” tremor, especially in hands
- Rigidity: lead-pipe rigidity with cogwheeling due to superimposed tre



Clinical Picture

Negative motor

- **Bradykinesia**: slow, small amplitude movements, fatiguing of rapid alternating movements, difficulty initiating movement
- ***Related findings***: masked facies, hypophonia, (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing

Freezing:

- It occurs with walking triggered by initiating stride or barriers/destinations, lasting seconds

Postural instability:

- Late finding presenting as falls, festinating gait

Clinical Picture

Cognition:

- Bradyphrenia (slow to think/respond), dementia (late finding)

Behavioural:

- Decreased spontaneous speech, depression, sleep disturbances, anxiety

Autonomic:

- Constipation, urinary retention, sexual dysfunction, later findings of orthostatic hypotension

When to suspect atypical or secondary parkinsonism?

Lack of tremor	Various Parkinson's-plus syndromes
Early postural instability and falls	Progressive Supranuclear Palsy (PSP)
Early dysphagia	Corticobasal degeneration (CBD)
Early dementia or hallucinations	Dementia with Lewy body (DLB)
Early or severe dysautonomia	Multi System Atrophy (MSA)
Associated unexplained liver disease	Wilson's disease
Antipsychotic exposure	Drug-induced
Acute onset and/or non-progressive	Vascular

Clinical vignette

- A 50-year-old man presents with a 2-year history of tremors of the both hands that disappear with voluntary movement. He has no past medical history and takes no medications.
- Review of systems is positive for anhidrosis and a 5-year history of impotence. He also give history of urinary frequency, urgency, and occasional incontinence.
- On physical examination, He is alert and oriented and has resting tremor of his hands that has a “pill rolling” quality. His face is expressionless (mask-like) and his movements are slow. He has difficulty getting out of a chair. There is a decrease in tone and strength of the extremities.

Clinical reasoning

What are features of Parkinson's disease?

- Tremors
- Bradykinesia

What are the atypical features?

- Early age of onset.
- Bilateral tremors at the onset
- Autonomic manifestations
  - ✓ Urinary symptoms
  - ✓ Impotence
- Decreased muscle tone and strength

Atypical features = Parkinson plus syndromes

Prominent autonomic manifestations suggestive of Multiple System Atrophy (MSA)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القوات المسلحة المصرية
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Management

Management

1- Medical treatment

2- Surgical treatment

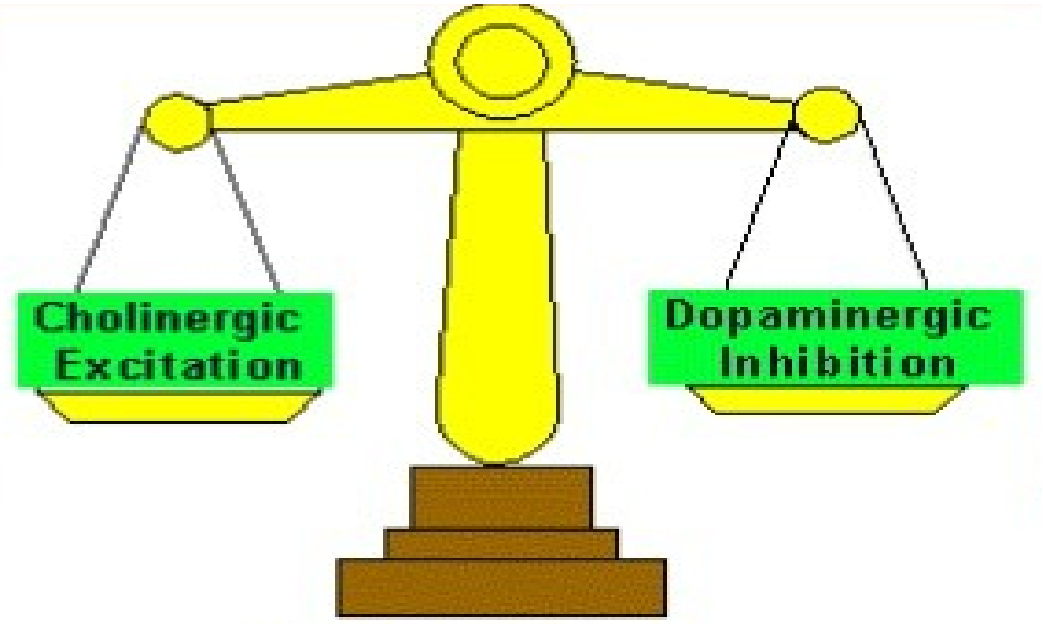
- **Lesion in GPi (Pallidotomy) or subthalamic nuclie**
- **Implantation of electrodes**

3- Implantation of dopamine-secreting tissue

Strategy of medical treatment

There is no cure, the aim of pharmacological therapy is to provide symptomatic relief

Restoring DA/Ach balance



Strategy of treatment

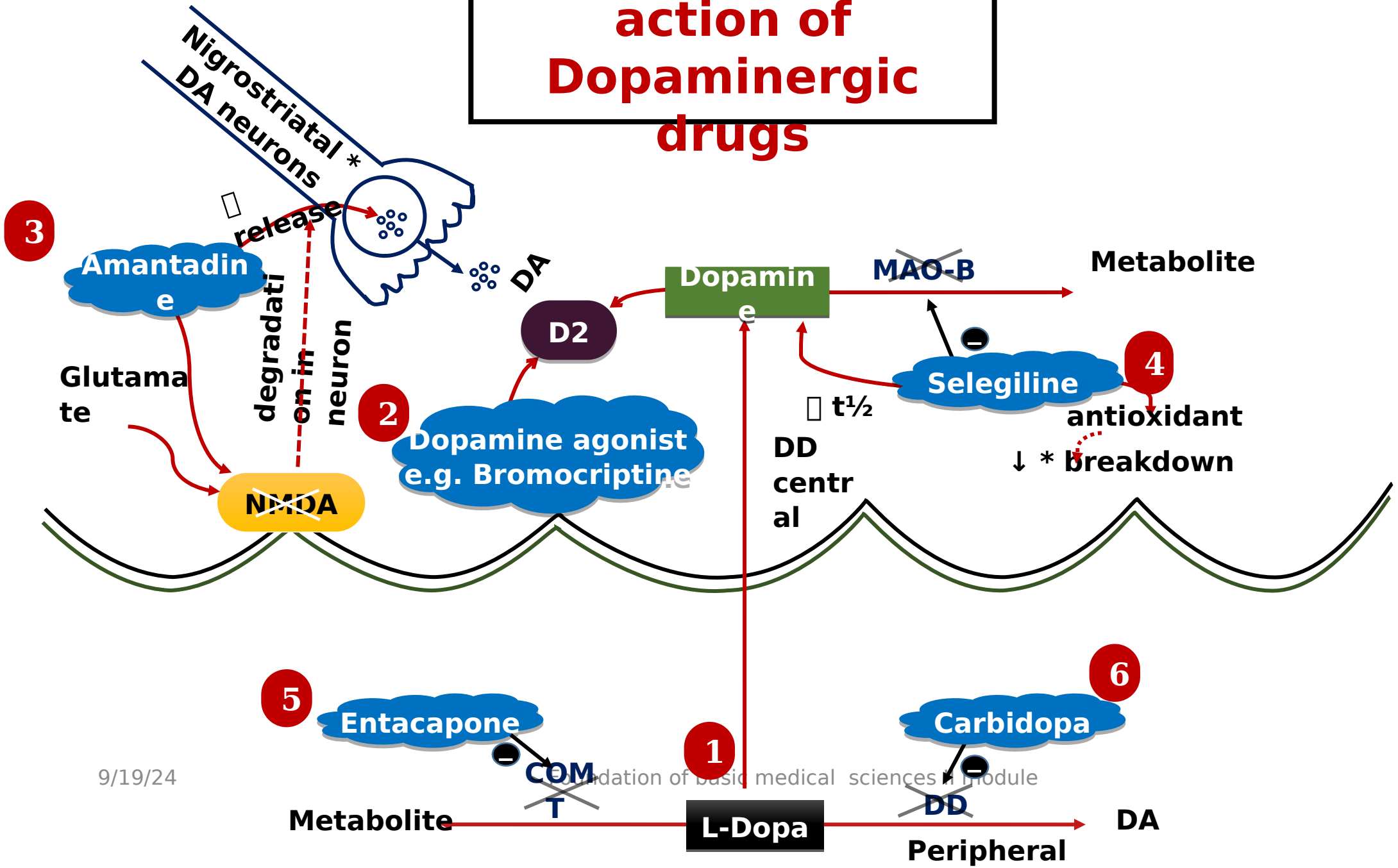
↑ DA

- **Levodopa/carbidopa.**
- **DA agonists**
  (ergot): Bromocriptine
  (non-ergot): Pramipexole
- **Amantadine**.
- **COMT inhibitors:**Entacapone.
- **MAO-B inhibitors:**Selegiline-Rasagiline.

↓ Ach

- **Anticholinergics**:Benztropine

Mechanism of action of Dopaminergic drugs



I) Dopaminergic drugs

Most effecti ve

1) Levo dopa/ Carbidopa

Main stay of therapy

Mechanism of action:

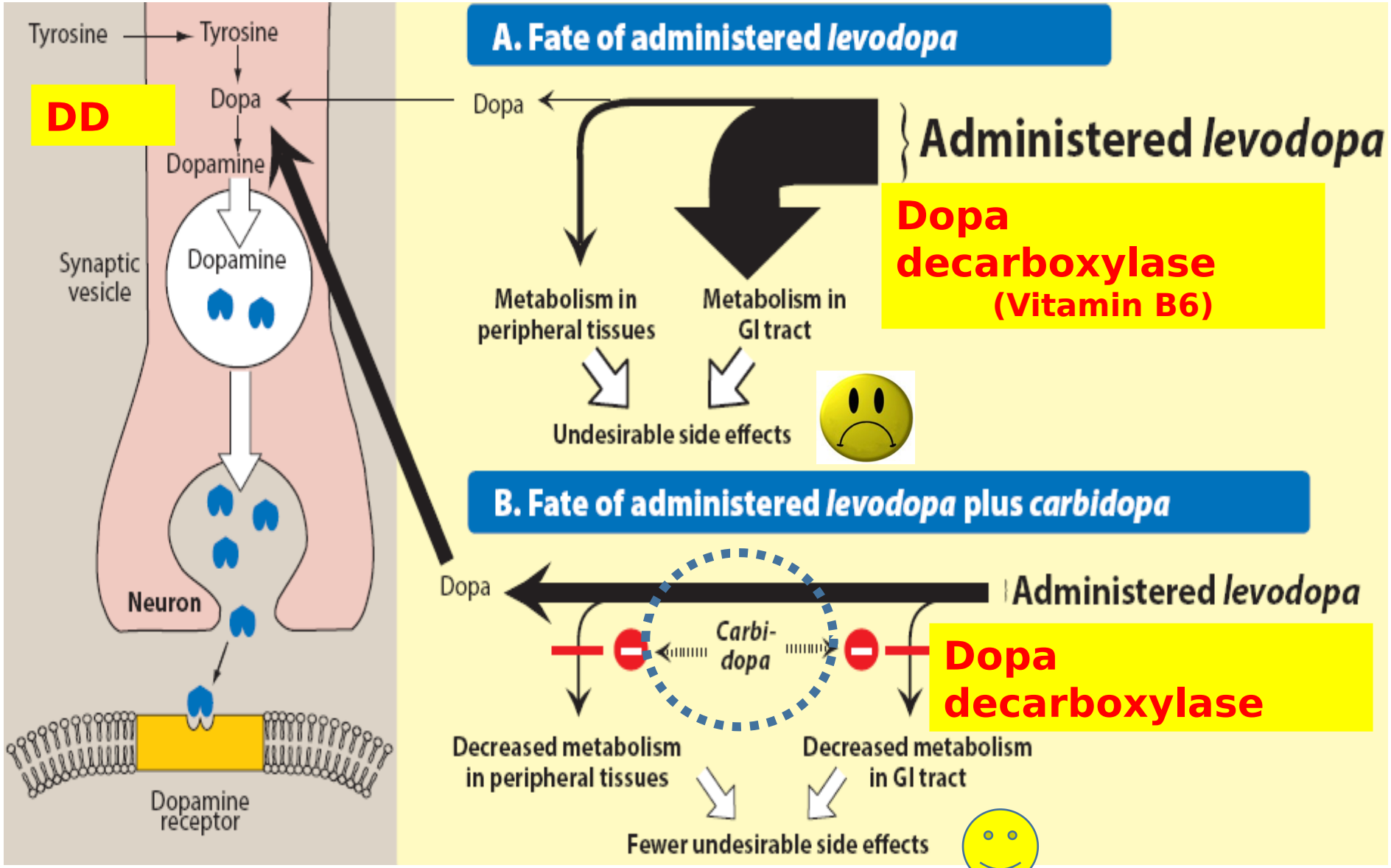
Levo dopa

- An immediate **precursor of DA** which **crosses BBB** (DA can not) converted **centrally** via **Dopa Decarboxylase (DD)** enzyme into **DA**.

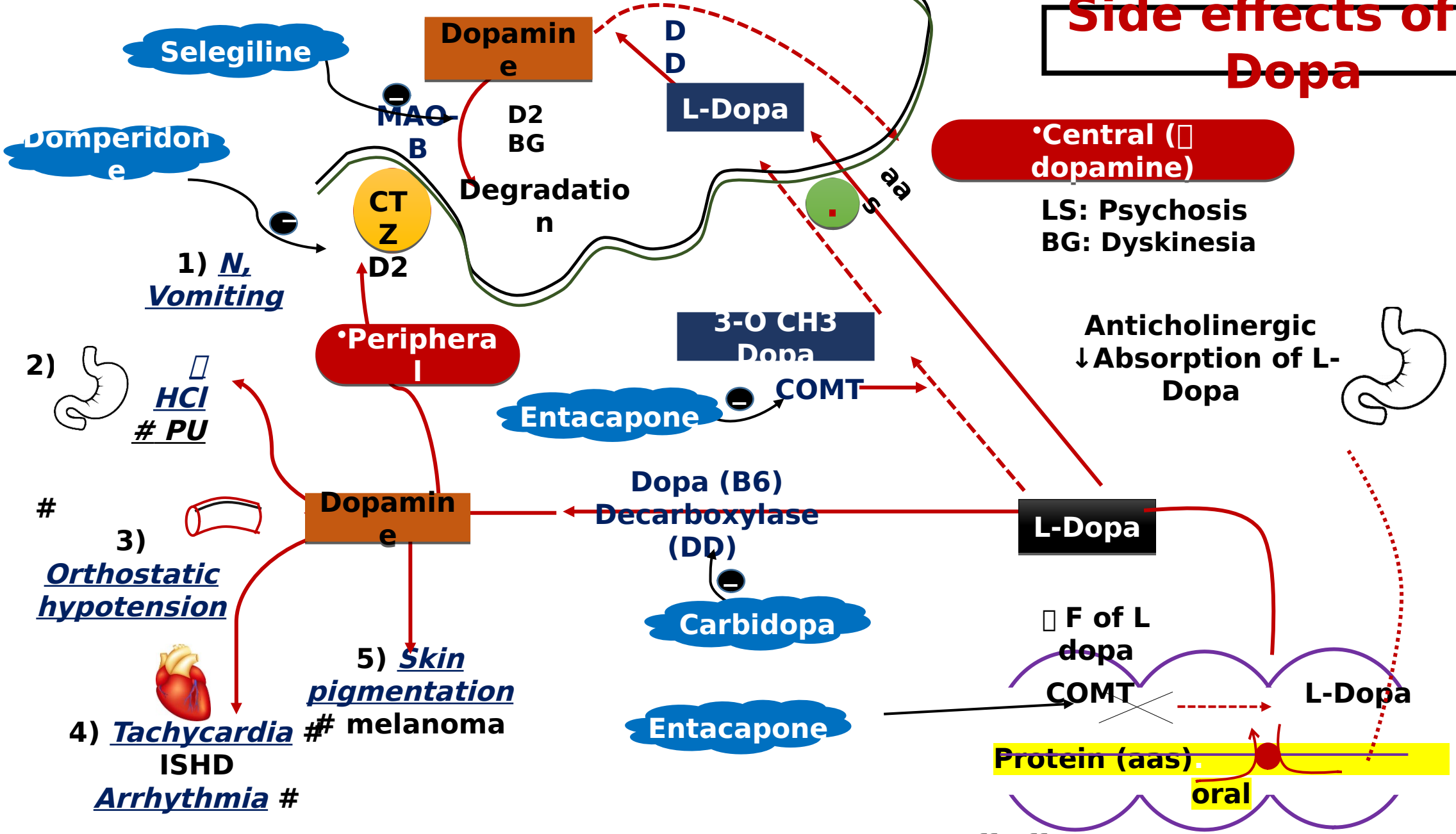
Carbidopa

- Without *carbidopa*, much of levodopa is decarboxylated to DA in the periphery, resulting in peripheral adverse effects.
- **Carbidopa**, a **peripheral Dopa Decarboxylase enzyme** inhibitor → ↓ levodopa metabolism peripherally → ↑ its availability centrally.

Levo dopa/ Carbidopa

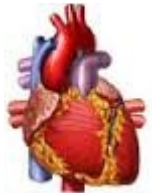


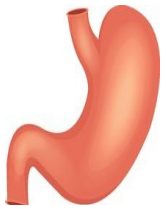
Side effects of L-Dopa

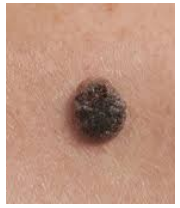


- Fluctuation in response
  - on-off effect
  - End of dose akinesia (wearing off)

Adverse effects of levodopa:





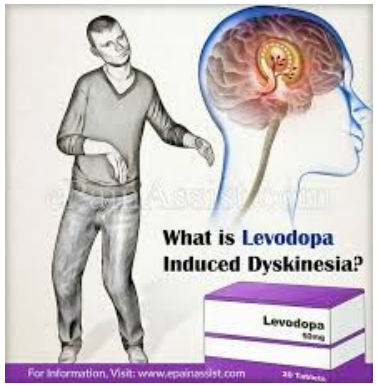


A) Peripheral(↓withcarbidopa)

- GIT: Anorexia, nausea, and vomiting (CTZ stimulation),HCl (# PU)
- CVS: postural hypotension and arrhythmias(# ISHD)
- Skin: skin pigmentation (# malignant melanoma)

B) Central(↑withcarbidopa)

- Confusion, Hallucinations, psychosis (especially in theelderly)
- Abnormal involuntary movements (dyskinesias) (↑DA in basal ganglia)



C) Fluctuations in response

- End of dose akinesia
- On-off effect

Management of L-dopa induced nausea & vomiting

Metoclopramide

- Blocks DA receptors both peripherally and centrally

Domperidone

- Blocks DA receptors peripherally, not centrally

Advantages of combination of carbidopa with levodopa:

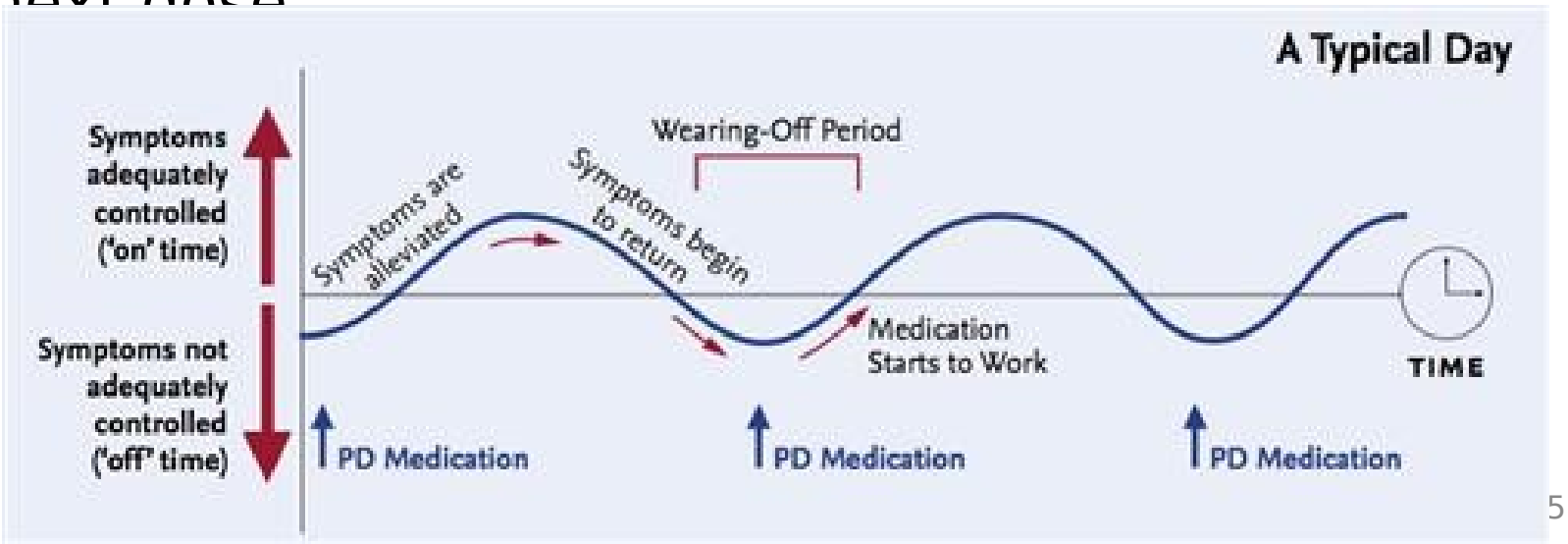
1. Lowers the daily dose of levodopa by four- to fivefold
2. Decreases the severity of the peripheral side effects
3. Increases the central effect

Fluctuation of L Dopa response:

Levodopa has a short half-life (1 to 2 hours), which causes:

1- “On–off” effect (sudden swings from mobility to bradykinesia)

2- **End of dose Akinesia** (gradual loss of effect (Wearing off) before the next dose



Contraindications with L-Dopa

- Narrow-angle glaucoma (severe mydriasis → aggravate glaucoma)
- Patients with a history of cardiac arrhythmias or recent cardiac infarction
- Nonselective MAO inhibitors (tranylcypromine) can precipitate hypertensive crisis and hyperpyrexia

Diet and L DOPA:

Ingestion of high protein interferes with the action of levodopa

(AA competes with L DOPA for absorption and CNS uptake)

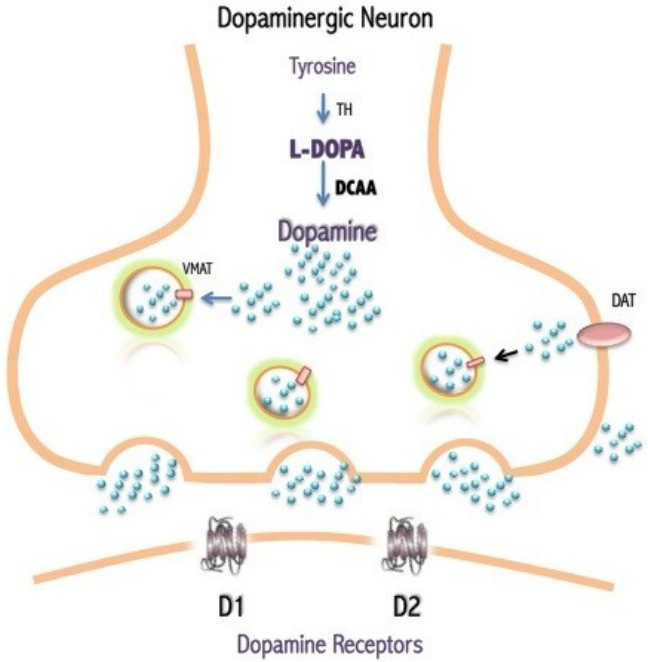
Levodopa therefore should be administere
at least 30 minutes before meals

Vitamin B6

→ ↑ peripheral decarboxylation of levod
↓ its effectiveness

Drug induced parkinsonism:

- **Antipsychotics**: block D2 receptors
- **Reserpine**: depletes DA stores
- **Methyl dopa**: ↓ DA synthesis



Lecture Quiz

Parkinson's disease:

a. is caused by a lesion in the posteroventral nucleus of the thalamus.

b. is caused by a lesion in the substantia nigra and globus pallidus.

c. is accompanied by kinetic tremors.

d. is accompanied by clasp-knife rigidity.

Quiz

- The following is not an expected adverse effect after L-dopa administration:
  a) Skin pigmentation
  b) Orthostatic hypotension
  c) May precipitate peptic ulcer
  d) Bronchial asthma
  e) Dyskinesia

SUGGESTED TEXTBOOKS

1. **Guyton and Hall Textbook of Medical Physiology.**
   https://www.amazon.com/Guyton-Hall-Textbook-Medical-Physiology/dp/1455770051

2. **Ganong's Review of Medical Physiology, 25e.**

   https://www.amazon.com/Ganongs-Review-Medical-Physiology-Twenty-Fifth/dp/007182510X

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

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- Kumar, Vinay, and Abbas, Abul K, and Aster: Robbins Basic Pathology, 10th)ed. (2018) Pages 851-876
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Thank
You!